



## Clinical trial results:

**A Phase I/II study to evaluate the safety and pharmacokinetics of intravenous Trappsol® Cyclo™ (HP-Beta-CD) in patients with Niemann-Pick disease type C (NPC-1) and the pharmacodynamic effects of treatment upon markers of cholesterol metabolism and clinical outcomes**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-005761-23 |
| Trial protocol           | GB SE IT       |
| Global end of trial date | 03 March 2021  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 23 July 2022 |
| First version publication date | 23 July 2022 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CTD-TCNPC-201 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02912793 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Cyclo Therapeutics, Inc.  |
| Sponsor organisation address | 6714 NW 16th Street, Suite B, Gainesville, United States, FL 32653            |
| Public contact               | Lise Kjems, MD PhD, CMO, Cyclo Therapeutics, Inc.,<br>lise.kjems@cyclodex.com |
| Scientific contact           | Lise Kjems, MD PhD, CMO, Cyclo Therapeutics, Inc.,<br>lise.kjems@cyclodex.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 03 March 2021 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 03 March 2021 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 03 March 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

Stage 1

- To compare the plasma pharmacokinetics of hydroxypropyl- $\beta$ -cyclodextrin following three different single doses of intravenous Trappsol® in patients with NPC-1

Stage 2

- To evaluate the efficacy and tolerability of three different doses of Trappsol® in the management of clinical manifestations of NPC-1

Protection of trial subjects:

This study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki (October 2013), or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Safety of the subjects was safeguarded through safety data review throughout the study.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 26 September 2016 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Sweden: 1         |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Israel: 6         |
| Worldwide total number of subjects   | 12                |
| EEA total number of subjects         | 1                 |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

|                           |   |
|---------------------------|---|
| Children (2-11 years)     | 8 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years)      | 3 |
| From 65 to 84 years       | 0 |
| 85 years and over         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

First patient in on 20th Jun 2017 and last patient out on 3rd Mar 2021. All patients recruited to hospital clinics.

### Pre-assignment

Screening details:

13 patients were screened for up to 28 days before entry. One patient was excluded due to screen failure.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 13 <sup>[1]</sup> |
| Number of subjects completed | 12                |

### Pre-assignment subject non-completion reasons

|                            |                     |
|----------------------------|---------------------|
| Reason: Number of subjects | Failed screening: 1 |
|----------------------------|---------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: 13 patients were screened for up to 28 days before entry. One patient was excluded due to screen failure.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall trial (overall period)                      |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                             |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer |

Blinding implementation details:

Study drug was prepared by an on-site pharmacist; therefore, the blind for the Principal Investigator, site personnel and patient could be maintained. PK bioanalytical personnel and drug accountability monitors were unblinded.

### Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | Trappsol® Cyclo™ IV 1500 mg/kg |

Arm description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.

|  |                       |
|--|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Trappsol® Cyclo™      |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks at a dose of 1500 mg/kg.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Trappsol® Cyclo™ IV 2000 mg/kg |
|------------------|--------------------------------|

Arm description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.

|  |                       |
|--|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Trappsol® Cyclo™      |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks at a dose of 2000 mg/kg.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Trappsol® Cyclo™ IV 2500 mg/kg |
|------------------|--------------------------------|

**Arm description:**

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks

|  |                       |
|--|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Trappsol® Cyclo™      |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks at a dose of 2500 mg/kg.

| <b>Number of subjects in period 1</b>      | Trappsol® Cyclo™<br>IV 1500 mg/kg | Trappsol® Cyclo™<br>IV 2000 mg/kg | Trappsol® Cyclo™<br>IV 2500 mg/kg |
|--|-----------------------------------|-----------------------------------|-----------------------------------|
| Started                                    | 5                                 | 4                                 | 3                                 |
| Completed                                  | 2                                 | 4                                 | 3                                 |
| Not completed                              | 3                                 | 0                                 | 0                                 |
| Physician decision                         | 1                                 | -                                 | -                                 |
| Consent withdrawn by subject               | 1                                 | -                                 | -                                 |
| Unable to travel due to Covid restrictions | 1                                 | -                                 | -                                 |

## Baseline characteristics

### Reporting groups

|   |                                |
|---|--------------------------------|
| Reporting group title   | Trappsol® Cyclo™ IV 1500 mg/kg |
| Reporting group description:<br>HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks. |                                |
| Reporting group title   | Trappsol® Cyclo™ IV 2000 mg/kg |
| Reporting group description:<br>HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks. |                                |
| Reporting group title   | Trappsol® Cyclo™ IV 2500 mg/kg |
| Reporting group description:<br>HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks  |                                |

| Reporting group values   | Trappsol® Cyclo™ IV 1500 mg/kg | Trappsol® Cyclo™ IV 2000 mg/kg | Trappsol® Cyclo™ IV 2500 mg/kg |
|--|--------------------------------|--------------------------------|--------------------------------|
| Number of subjects   | 5                              | 4                              | 3                              |
| Age categorical<br>Units: Subjects   |                                |                                |                                |
| Children (2-11 years)  | 3                              | 3                              | 2                              |
| Adolescents (12-17 years)  | 1                              | 0                              | 0                              |
| Adults (18-64 years)   | 1                              | 1                              | 1                              |
| Age continuous<br>Units: years   |                                |                                |                                |
| arithmetic mean  | 12.2                           | 13.5                           | 10.7                           |
| full range (min-max)   | 2 to 34                        | 2 to 39                        | 3 to 21                        |
| Gender categorical<br>Units: Subjects  |                                |                                |                                |
| Female   | 3                              | 1                              | 1                              |
| Male   | 2                              | 3                              | 2                              |
| Race<br>Units: Subjects  |                                |                                |                                |
| White  | 4                              | 4                              | 3                              |
| Black/African  | 1                              | 0                              | 0                              |
| Weight<br>Units: Kg  |                                |                                |                                |
| arithmetic mean  | 25                             | 34.5                           | 30.0                           |
| full range (min-max)   | 11 to 58                       | 13 to 68                       | 15 to 45                       |
| 17-Domain Niemann-Pick disease Type C-Clinical Severity Scale<br>Units: Points on scale 0-61 |                                |                                |                                |
| arithmetic mean  | 21.0                           | 15.5                           | 17.7                           |
| standard deviation   | ± 9.25                         | ± 7.42                         | ± 5.69                         |
| <b>Reporting group values</b>  | Total                          |                                |                                |
| Number of subjects   | 12                             |                                |                                |

|   |    |  |  |
|---|----|--|--|
| Age categorical<br>Units: Subjects  |    |  |  |
| Children (2-11 years)   | 8  |  |  |
| Adolescents (12-17 years)   | 1  |  |  |
| Adults (18-64 years)  | 3  |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>full range (min-max)   | -  |  |  |
| Gender categorical<br>Units: Subjects   |    |  |  |
| Female  | 5  |  |  |
| Male  | 7  |  |  |
| Race<br>Units: Subjects   |    |  |  |
| White   | 11 |  |  |
| Black/African   | 1  |  |  |
| Weight<br>Units: Kg<br>arithmetic mean<br>full range (min-max)  | -  |  |  |
| 17-Domain Niemann-Pick disease Type C-Clinical Severity Scale<br>Units: Points on scale 0-61<br>arithmetic mean<br>standard deviation | -  |  |  |

## End points

### End points reporting groups

|  |                                |
|--|--------------------------------|
| Reporting group title  | Trappsol® Cyclo™ IV 1500 mg/kg |
| Reporting group description:<br>HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.  |                                |
| Reporting group title  | Trappsol® Cyclo™ IV 2000 mg/kg |
| Reporting group description:<br>HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.  |                                |
| Reporting group title  | Trappsol® Cyclo™ IV 2500 mg/kg |
| Reporting group description:<br>HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks   |                                |
| Subject analysis set title   | Across the dose range          |
| Subject analysis set type  | Intention-to-treat             |
| Subject analysis set description:<br>All patients who were assigned to a treatment regimen (randomized, even if not dosed) constituted the ITT population. The ITT population was analyzed using the treatment assigned in the randomization schedule even if a patient was dosed incorrectly. |                                |

### Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (C<sub>max</sub>)

|  |  |
|--|--|
| End point title  | To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (C <sub>max</sub> ) <sup>[1]</sup> |
| End point description:<br>To evaluate plasma PK of Trappsol® by comparison of Maximum Concentration (C <sub>max</sub> ) of the three doses.  |  |
| End point type   | Primary  |
| End point timeframe:<br>0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion   |  |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included. |  |

| End point values                     | Trappsol® Cyclo™ IV 1500 mg/kg | Trappsol® Cyclo™ IV 2000 mg/kg | Trappsol® Cyclo™ IV 2500 mg/kg |  |
|--------------------------------------|--------------------------------|--------------------------------|--------------------------------|--|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                |  |
| Number of subjects analysed          | 5                              | 3 <sup>[2]</sup>               | 3                              |  |
| Units: ng/ml                         |                                |                                |                                |  |
| arithmetic mean (standard deviation) | 1272600 (± 489692)             | 1856667 (± 803140)             | 1920000 (± 121655)             |  |

Notes:

[2] - Sample missing for 1 patient

### Statistical analyses

No statistical analyses for this end point



**Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Tmax)**

|                 |   |
|-----------------|---|
| End point title | To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Tmax) <sup>[3]</sup> |
|-----------------|---|

End point description:

To evaluate plasma PK of Trappsol® by comparison of time to maximum concentration (tmax) of the three doses

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

| End point values                     | Trappsol®<br>Cyclo™ IV<br>1500 mg/kg | Trappsol®<br>Cyclo™ IV<br>2000 mg/kg | Trappsol®<br>Cyclo™ IV<br>2500 mg/kg |  |
|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type                   | Reporting group                      | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed          | 5                                    | 3                                    | 3                                    |  |
| Units: hours                         |                                      |                                      |                                      |  |
| arithmetic mean (standard deviation) | 5.66 (± 1.7)                         | 6.7 (± 1.16)                         | 6.02 (± 0.03)                        |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Vd)**

|                 |   |
|-----------------|---|
| End point title | To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Vd) <sup>[4]</sup> |
|-----------------|---|

End point description:

To evaluate plasma PK of Trappsol® by comparison of volume of distribution (Vd) of the three doses

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

| End point values            | Trappsol®<br>Cyclo™ IV<br>1500 mg/kg | Trappsol®<br>Cyclo™ IV<br>2000 mg/kg | Trappsol®<br>Cyclo™ IV<br>2500 mg/kg |  |
|-----------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type          | Reporting group                      | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed | 5                                    | 3                                    | 3                                    |  |
| Units: ml/kg                |                                      |                                      |                                      |  |
| median (standard deviation) | 426 (± 168)                          | 399 (± 193)                          | 412 (± 107)                          |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (T1/2)

|                        |  |
|------------------------|--|
| End point title        | To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (T1/2) <sup>[5]</sup>      |
| End point description: | Plasma elimination half-life (T1/2)  |
| End point type         | Primary  |
| End point timeframe:   | 0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion |

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

| End point values                     | Trappsol®<br>Cyclo™ IV<br>1500 mg/kg | Trappsol®<br>Cyclo™ IV<br>2000 mg/kg | Trappsol®<br>Cyclo™ IV<br>2500 mg/kg |  |
|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type                   | Reporting group                      | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed          | 5                                    | 3                                    | 3                                    |  |
| Units: Hours                         |                                      |                                      |                                      |  |
| arithmetic mean (standard deviation) | 2.01 (± 0.27)                        | 1.63 (± 0.15)                        | 1.81 (± 0.259)                       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: To Evaluate the Cerebrospinal fluid (CSF) Pharmacokinetics of 3 Doses of Trappsol® (Concentration of HP-β-CD in the CSF)

|                        |   |
|------------------------|---|
| End point title        | To Evaluate the Cerebrospinal fluid (CSF) Pharmacokinetics of 3 Doses of Trappsol® (Concentration of HP-β-CD in the CSF) <sup>[6]</sup> |
| End point description: | To evaluate Concentration of HP-β-CD in the CSF of the three doses of Trappsol®   |
| End point type         | Primary   |
| End point timeframe:   | 8 hour after start of 1st Infusion  |

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

| End point values                       | Trappsol®<br>Cyclo™ IV<br>1500 mg/kg | Trappsol®<br>Cyclo™ IV<br>2000 mg/kg | Trappsol®<br>Cyclo™ IV<br>2500 mg/kg |  |
|--|--------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type                     | Reporting group                      | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed            | 2                                    | 4                                    | 2                                    |  |
| Units: ng/mL                           |                                      |                                      |                                      |  |
| arithmetic mean (full range (min-max)) | 232600 (22200 to 443000)             | 22225 (0 to 48800)                   | 184400 (16800 to 352000)             |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: To Evaluate CSF to Plasma ratio of 3 doses of Trappsol®

|                 |  |
|-----------------|--|
| End point title | To Evaluate CSF to Plasma ratio of 3 doses of Trappsol® <sup>[7]</sup> |
|-----------------|--|

End point description:

The mean ratio of CSF HP-β-CD concentration to plasma HP-β-CD concentration in the three reporting groups

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

| End point values                     | Trappsol®<br>Cyclo™ IV<br>1500 mg/kg | Trappsol®<br>Cyclo™ IV<br>2000 mg/kg | Trappsol®<br>Cyclo™ IV<br>2500 mg/kg |  |
|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type                   | Reporting group                      | Reporting group                      | Reporting group                      |  |
| Number of subjects analysed          | 3 <sup>[8]</sup>                     | 4 <sup>[9]</sup>                     | 3 <sup>[10]</sup>                    |  |
| Units: Ratio                         |                                      |                                      |                                      |  |
| arithmetic mean (standard deviation) | 0.215 (± 0.353)                      | 0.0608 (± 0.124)                     | 0.196 (± 0.157)                      |  |

Notes:

[8] - 7 samples from 3 participants

[9] - 8 samples from 4 participants

[10] - 4 samples from 3 participants

### Statistical analyses

No statistical analyses for this end point

### Secondary: To Evaluate the Effect of Treatment on Plasma Biomarkers of NPC disease

|                 |   |
|-----------------|---|
| End point title | To Evaluate the Effect of Treatment on Plasma Biomarkers of NPC disease |
|-----------------|---|

End point description:

Niemann-Pick disease type C (NPC-1)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

| End point values                     | Across the dose range |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 2                     |  |  |  |
| Units: % Change from baseline        |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| Lysosphingomyelin 509                | 61.3 (± 17.7)         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: To Evaluate the Effect of Treatment on Biomarkers of Cholesterol Metabolism (Serum Lathosterol, 27-hydroxycholesterol, 24S-hydroxycholesterol)

|                 |  |
|-----------------|--|
| End point title | To Evaluate the Effect of Treatment on Biomarkers of Cholesterol Metabolism (Serum Lathosterol, 27-hydroxycholesterol, 24S-hydroxycholesterol) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Various times post dosing (Day 3 post dose)

| End point values                     | Across the dose range |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 7                     |  |  |  |
| Units: Mean % of baseline            |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| Lathosterol                          | 59.11 (± 13.45)       |  |  |  |
| 27-hydroxycholesterol                | 199.19 (± 45.69)      |  |  |  |
| 24S-hydroxycholesterol               | 117.9 (± 6.74)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: To Evaluate the Effect of Treatment on Biomarkers of Cholesterol

## Metabolism (LDL and HDL cholesterol)

|                 |   |
|-----------------|---|
| End point title | To Evaluate the Effect of Treatment on Biomarkers of Cholesterol Metabolism (LDL and HDL cholesterol) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Various times post dosing (Day 3 post dose)

| End point values                     | Across the dose range |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 12                    |  |  |  |
| Units: Mmol/L                        |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| LDL cholesterol                      | 4.06 (± 0.83)         |  |  |  |
| HDL cholesterol                      | 1.35 (± 0.24)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: To Evaluate the Effect of Treatment on CSF Biomarkers of NPC disease

|                 |  |
|-----------------|--|
| End point title | To Evaluate the Effect of Treatment on CSF Biomarkers of NPC disease |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 48

| End point values                       | Across the dose range  |  |  |  |
|--|------------------------|--|--|--|
| Subject group type                     | Subject analysis set   |  |  |  |
| Number of subjects analysed            | 2                      |  |  |  |
| Units: % baseline                      |                        |  |  |  |
| arithmetic mean (full range (min-max)) |                        |  |  |  |
| CSF Tau                                | 48.83 (28.11 to 69.56) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: To Evaluate the Effect of Treatment on NIH NPC severity scale 17

|  |  |
|--|--|
| End point title  | To Evaluate the Effect of Treatment on NIH NPC severity scale 17 |
| End point description:<br>NIH NPC severity scale (NCSS) (17 item) and Clinical Global Impression (CGI-I) |  |
| End point type   | Secondary  |
| End point timeframe:<br>NIH NPC severity scale Week 48, CGI Week 12 and Week 48                          |  |

| End point values                     | Across the dose range |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 12 <sup>[11]</sup>    |  |  |  |
| Units: Mean Score                    |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| NCSS Mean total score                | 17.3 ( $\pm$ 5.97)    |  |  |  |
| CGI-I Mean score w 12                | 2.9 ( $\pm$ 0.89)     |  |  |  |
| CGI-I Mean score End of study        | 2.7 ( $\pm$ 1.0)      |  |  |  |

Notes:

[11] - 11 subjects analysed for CGI-I mean score

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: To Evaluate the Effect of Treatment on Liver and Spleen Morphology

|   |  |
|---|--|
| End point title   | To Evaluate the Effect of Treatment on Liver and Spleen Morphology |
| End point description:<br>Measure of organ length by ultrasound |  |
| End point type  | Other pre-specified  |
| End point timeframe:<br>Change from baseline to end of study    |  |

| End point values                     | Across the dose range |  |  |  |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type                   | Subject analysis set  |  |  |  |
| Number of subjects analysed          | 8 <sup>[12]</sup>     |  |  |  |
| Units: Cm                            |                       |  |  |  |
| arithmetic mean (standard deviation) |                       |  |  |  |
| Change in liver size                 | -0.198 ( $\pm$ 1.235) |  |  |  |
| Change in spleen size                | -1.22 ( $\pm$ 1.415)  |  |  |  |

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Notes:

[12] - 6 subjects analysed for change in spleen size

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### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were continuously monitored throughout the study from signing of the ICF until the last follow-up assessment

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.1   |

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Trappsol® Cyclo™ IV 1500 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Trappsol® Cyclo™ IV 2000 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Trappsol® Cyclo™ IV 2500 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks

| Serious adverse events                            | Trappsol® Cyclo™ IV 1500 mg/kg | Trappsol® Cyclo™ IV 2000 mg/kg | Trappsol® Cyclo™ IV 2500 mg/kg |
|---|--------------------------------|--------------------------------|--------------------------------|
| Total subjects affected by serious adverse events |                                |                                |                                |
| subjects affected / exposed                       | 2 / 5 (40.00%)                 | 1 / 4 (25.00%)                 | 2 / 3 (66.67%)                 |
| number of deaths (all causes)                     | 0                              | 0                              | 0                              |
| number of deaths resulting from adverse events    | 0                              | 0                              | 0                              |
| Nervous system disorders                          |                                |                                |                                |
| Loss of consciousness                             |                                |                                |                                |
| subjects affected / exposed                       | 1 / 5 (20.00%)                 | 0 / 4 (0.00%)                  | 0 / 3 (0.00%)                  |
| occurrences causally related to treatment / all   | 0 / 1                          | 0 / 0                          | 0 / 0                          |
| deaths causally related to treatment / all        | 0 / 0                          | 0 / 0                          | 0 / 0                          |
| Seizure   |                                |                                |                                |
| subjects affected / exposed                       | 1 / 5 (20.00%)                 | 0 / 4 (0.00%)                  | 0 / 3 (0.00%)                  |
| occurrences causally related to treatment / all   | 0 / 7                          | 0 / 0                          | 0 / 0                          |
| deaths causally related to treatment / all        | 0 / 0                          | 0 / 0                          | 0 / 0                          |
| Cerebrospinal fluid leakage                       |                                |                                |                                |



|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Peripheral swelling                                  |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Ear and labyrinth disorders                          |                |                |                |
| Hypoacusis   |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Pneumonia aspiration                                 |                |                |                |
| subjects affected / exposed                          | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders               |                |                |                |
| Erythema   |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                          |                |                |                |
| Influenza/Influenza B                                |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Tonsillitis  |                |                |                |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Trappsol® Cyclo™<br>IV 1500 mg/kg | Trappsol® Cyclo™<br>IV 2000 mg/kg | Trappsol® Cyclo™<br>IV 2500 mg/kg |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events |                                   |                                   |                                   |
| subjects affected / exposed                           | 5 / 5 (100.00%)                   | 4 / 4 (100.00%)                   | 3 / 3 (100.00%)                   |
| General disorders and administration site conditions  |                                   |                                   |                                   |
| Pyrexia   |                                   |                                   |                                   |
| subjects affected / exposed                           | 1 / 5 (20.00%)                    | 0 / 4 (0.00%)                     | 3 / 3 (100.00%)                   |
| occurrences (all)                                     | 1                                 | 0                                 | 5                                 |
| Fatigue   |                                   |                                   |                                   |
| subjects affected / exposed                           | 0 / 5 (0.00%)                     | 1 / 4 (25.00%)                    | 1 / 3 (33.33%)                    |
| occurrences (all)                                     | 0                                 | 1                                 | 2                                 |
| Peripheral Swelling                                   |                                   |                                   |                                   |
| subjects affected / exposed                           | 0 / 5 (0.00%)                     | 1 / 4 (25.00%)                    | 0 / 3 (0.00%)                     |
| occurrences (all)                                     | 0                                 | 1                                 | 0                                 |
| Catheter Site Erythema                                |                                   |                                   |                                   |
| subjects affected / exposed                           | 0 / 5 (0.00%)                     | 0 / 4 (0.00%)                     | 1 / 3 (33.33%)                    |
| occurrences (all)                                     | 0                                 | 0                                 | 1                                 |
| Catheter Site Rash                                    |                                   |                                   |                                   |
| subjects affected / exposed                           | 0 / 5 (0.00%)                     | 0 / 4 (0.00%)                     | 1 / 3 (33.33%)                    |
| occurrences (all)                                     | 0                                 | 0                                 | 1                                 |
| Gait Disturbance                                      |                                   |                                   |                                   |
| subjects affected / exposed                           | 0 / 5 (0.00%)                     | 0 / 4 (0.00%)                     | 1 / 3 (33.33%)                    |
| occurrences (all)                                     | 0                                 | 0                                 | 1                                 |
| Respiratory, thoracic and mediastinal disorders       |                                   |                                   |                                   |
| Cough   |                                   |                                   |                                   |
| subjects affected / exposed                           | 3 / 5 (60.00%)                    | 1 / 4 (25.00%)                    | 2 / 3 (66.67%)                    |
| occurrences (all)                                     | 3                                 | 2                                 | 7                                 |
| Rhinorrhoea   |                                   |                                   |                                   |
| subjects affected / exposed                           | 1 / 5 (20.00%)                    | 1 / 4 (25.00%)                    | 0 / 3 (0.00%)                     |
| occurrences (all)                                     | 1                                 | 1                                 | 0                                 |
| Epistaxis   |                                   |                                   |                                   |
| subjects affected / exposed                           | 0 / 5 (0.00%)                     | 0 / 4 (0.00%)                     | 1 / 3 (33.33%)                    |
| occurrences (all)                                     | 0                                 | 0                                 | 2                                 |
| Oropharyngeal Pain                                    |                                   |                                   |                                   |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Pneumonia Aspiration                 |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 2              | 0              | 0              |
| Tonsillar Hypertrophy                |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Wheezing                             |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 1              | 0              | 1              |
| Psychiatric disorders                |                |                |                |
| Mood swings                          |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0              |
| Investigations                       |                |                |                |
| Acoustic Stimulation Tests Abnormal  |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Alanine Aminotransferase Increased   |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1              | 1              | 0              |
| Aspartate Aminotransferase Increased |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1              | 6              | 0              |
| Blood Cholesterol Increased          |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Body Temperature Increased           |                |                |                |
| subjects affected / exposed          | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0              |
| High Density Lipoprotein Decreased   |                |                |                |
| subjects affected / exposed          | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0              |
| Low Density Lipoprotein Increased    |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                              | 0              | 1              | 0              |
| Platelet Count Decreased                       |                |                |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Weight Decreased                               |                |                |                |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                              | 1              | 0              | 0              |
| C-reactive protein increased                   |                |                |                |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                              | 1              | 0              | 0              |
| Electrocardiogram T wave amplitude decreased   |                |                |                |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                              | 1              | 0              | 0              |
| Gamma-glutamyltransferase increased            |                |                |                |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                              | 1              | 0              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Contusion                                      |                |                |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 1 / 3 (33.33%) |
| occurrences (all)                              | 0              | 1              | 3              |
| Fall   |                |                |                |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                              | 1              | 0              | 2              |
| Gastrostomy Tube Site Complication             |                |                |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 1 / 3 (33.33%) |
| occurrences (all)                              | 0              | 1              | 5              |
| Head Injury                                    |                |                |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                              | 0              | 1              | 0              |
| Laceration                                     |                |                |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Post Lumbar Puncture Syndrome                  |                |                |                |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Procedural Pain<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Procedural Vomiting<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Cardiac disorders<br>Pericardial Effusion<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Nervous system disorders<br>Seizure<br>subjects affected / exposed<br>occurrences (all)       | 2 / 5 (40.00%)<br>2 | 1 / 4 (25.00%)<br>2 | 1 / 3 (33.33%)<br>3 |
| Cataplexy<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 5 (20.00%)<br>2 | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>2 |
| Cerebrospinal Fluid Leakage<br>subjects affected / exposed<br>occurrences (all)               | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Ataxia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Dyskinesia<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Headache  |                     |                     |                     |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Petit Mal Epilepsy<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 2 / 3 (66.67%)<br>4 |
| Restless Legs Syndrome<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Speech Disorder<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 3 (33.33%)<br>2 |
| Ear and labyrinth disorders<br>Hypoacusis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 5 (20.00%)<br>1 | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Cerumen Impaction<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Eye disorders<br>Eye swelling<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 5 (20.00%)<br>2 | 0 / 4 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)          | 1 / 5 (20.00%)<br>3 | 3 / 4 (75.00%)<br>4 | 2 / 3 (66.67%)<br>5 |
| Diarrhoea   |                     |                     |                     |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 5 (20.00%) | 1 / 4 (25.00%) | 3 / 3 (100.00%) |
| occurrences (all)                               | 1              | 3              | 6               |
| Nausea  |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 4 (50.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                               | 0              | 4              | 0               |
| Abdominal Distension                            |                |                |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)   |
| occurrences (all)                               | 1              | 0              | 0               |
| Constipation                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)   |
| occurrences (all)                               | 1              | 0              | 0               |
| Frequent Bowel Movements                        |                |                |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)   |
| occurrences (all)                               | 5              | 0              | 0               |
| Pigmentation Lip                                |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                               | 0              | 1              | 0               |
| Skin and subcutaneous tissue disorders          |                |                |                 |
| Rash  |                |                |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 1 / 4 (25.00%) | 1 / 3 (33.33%)  |
| occurrences (all)                               | 5              | 1              | 1               |
| Erythema  |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 3 (33.33%)  |
| occurrences (all)                               | 0              | 0              | 2               |
| Swelling face                                   |                |                |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 3 (0.00%)   |
| occurrences (all)                               | 1              | 0              | 0               |
| Renal and urinary disorders                     |                |                |                 |
| Incontinence                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 1 / 3 (33.33%)  |
| occurrences (all)                               | 0              | 1              | 1               |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Back pain                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 4 (50.00%) | 0 / 3 (0.00%)   |
| occurrences (all)                               | 0              | 2              | 0               |
| Muscle twitching                                |                |                |                 |

|  |                     |                    |                    |
|--|---------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0 |
| Infections and infestations                      |                     |                    |                    |
| Upper Respiratory Tract Infection                |                     |                    |                    |
| subjects affected / exposed                      | 3 / 5 (60.00%)      | 1 / 4 (25.00%)     | 2 / 3 (66.67%)     |
| occurrences (all)                                | 4                   | 1                  | 3                  |
| Nasopharyngitis                                  |                     |                    |                    |
| subjects affected / exposed                      | 1 / 5 (20.00%)      | 1 / 4 (25.00%)     | 2 / 3 (66.67%)     |
| occurrences (all)                                | 1                   | 2                  | 3                  |
| Rhinitis   |                     |                    |                    |
| subjects affected / exposed                      | 2 / 5 (40.00%)      | 1 / 4 (25.00%)     | 1 / 3 (33.33%)     |
| occurrences (all)                                | 2                   | 4                  | 6                  |
| Tonsillitis                                      |                     |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)       | 1 / 4 (25.00%)     | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 1                  | 0                  |
| Viral Infection                                  |                     |                    |                    |
| subjects affected / exposed                      | 1 / 5 (20.00%)      | 1 / 4 (25.00%)     | 0 / 3 (0.00%)      |
| occurrences (all)                                | 1                   | 1                  | 0                  |
| Anal Fungal Infection                            |                     |                    |                    |
| subjects affected / exposed                      | 1 / 5 (20.00%)      | 0 / 4 (0.00%)      | 0 / 3 (0.00%)      |
| occurrences (all)                                | 1                   | 0                  | 0                  |
| Skin infection                                   |                     |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)       | 0 / 4 (0.00%)      | 1 / 3 (33.33%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |
| Urinary Tract Infection                          |                     |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)       | 1 / 4 (25.00%)     | 0 / 3 (0.00%)      |
| occurrences (all)                                | 0                   | 3                  | 0                  |
| Metabolism and nutrition disorders               |                     |                    |                    |
| Decreased Appetite                               |                     |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)       | 0 / 4 (0.00%)      | 1 / 3 (33.33%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 28 July 2016      | Version 2.0<br>Removal of VFSE;<br>correction to Figure 1 Study Schematic; correction of NCCS to NCSS;<br>AE causality changed from yes/no to unlikely, possibly, probably;<br>neurology testing and PBMCs added to Day 1 in Table of Assessments   |
| 06 September 2016 | Version 2.1<br>Expanded definition of effective contraception in exclusion criterion 11;<br>exclusion criterion 12 added breastfeeding females;<br>discontinuation criteria for CTCAE G3 ototoxicity and CTCAE G3 renal failure added;<br>change of "expected adverse events" to observed and SUSAR requirements added;<br>emergency unblinding process added |
| 18 October 2016   | Version 3.0, Protocol amendment 1<br>Updated as per SA1   |
| 09 May 2018       | Version 4.0, Protocol amendment 2<br>All NSA2 and SA2 changes added   |
| 21 November 2019  | Version 5.0, Protocol amendment 3<br>SWE - Addition of interim analysis;<br>change to EU representative;<br>IB version 4.0;<br>change of company name from CTD Holdings to Cyclo Therapeutics, Inc.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported